Abnormal calcium handling properties underlie familial hypertrophic cardiomyopathy pathology in patient-specific induced pluripotent stem cells.

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Authors: Feng Lan, Andrew S Lee, Ping Liang, Veronica Sanchez-Freire, Patricia K Nguyen, Li Wang, Leng Han, Michelle Yen, Yongming Wang, Ning Sun, Oscar J Abilez, Shijun Hu, Antje D Ebert, Enrique G Navarrete, Chelsey S Simmons, Matthew Wheeler, Beth Pruitt, Richard Lewis, Yoshinori Yamaguchi, Euan A Ashley, Donald M Bers, Robert C Robbins, Michael T Longaker, Joseph C Wu

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Public Summary:
Familial hypertrophic cardiomyopathy (HCM) is a prevalent hereditary cardiac disorder causing heart failure and rhythm abnormality and death. To understand the mechanisms underlying HCM development, we generated patient-specific induced pluripotent stem cell cardiomyocytes (iPSC-CMs) from a ten-member family cohort carrying a mutation (Arg663His) in the myosin heavy chain gene. Diseased iPSC-CMs recapitulated numerous aspects of the HCM phenotype including cellular enlargement and abnormal rhythm. Calcium imaging indicated dysregulation of calcium cycling and elevation in intracellular calcium as central mechanisms for disease pathogenesis. Pharmacological restoration of calcium homeostasis prevented development of heart muscle cell enlargement and irregular electrical properties. We anticipate that these findings will help elucidate the mechanisms underlying HCM development in patients and identify novel therapies for the disease.

Scientific Abstract:
Familial hypertrophic cardiomyopathy (HCM) is a prevalent hereditary cardiac disorder linked to arrhythmia and sudden cardiac death. While the causes of HCM have been identified as genetic mutations in the cardiac sarcomere, the pathways by which sarcomeric mutations engender myocyte hypertrophy and electrophysiological abnormalities are not understood. To elucidate the mechanisms underlying HCM development, we generated patient-specific induced pluripotent stem cell cardiomyocytes (iPSC-CMs) from a ten-member family cohort carrying a hereditary HCM missense mutation (Arg663His) in the MYH7 gene. Diseased iPSC-CMs recapitulated numerous aspects of the HCM phenotype including cellular enlargement and contractile arrhythmia at the single-cell level. Calcium (Ca^{2+}) imaging indicated dysregulation of Ca^{2+} cycling and elevation in intracellular Ca^{2+} ($[Ca^{2+}]_i$) are central mechanisms for disease pathogenesis. Pharmacological restoration of Ca^{2+} homeostasis prevented development of hypertrophy and electrophysiological irregularities. We anticipate that these findings will help elucidate the mechanisms underlying HCM development and identify novel therapies for the disease.